

NF- κ B/Bcl-2/Caspase 3信号通路与吲哚美辛作用机制的综述与假说：急性胰腺炎胃肠道功能受损的潜在机制研究

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摘 要

急性胰腺炎是一种严重的炎症性疾病, 可导致胃肠道功能障碍, 增加病死率。NF- κ B信号通路在急性胰腺炎的炎症反应中起关键作用, 其激活可诱导多种炎症因子和抗凋亡蛋白的表达, 加剧炎症并影响细胞存活。Bcl-2/Caspase 3信号通路也与急性胰腺炎的发展密切相关, 调节细胞凋亡过程。NF- κ B信号通路与Bcl-2/Caspase 3信号通路存在联系, NF- κ B的激活可影响Bcl-2家族蛋白的表达, 进而调控细胞凋亡。吲哚美辛是一种非甾体类抗炎药, 已被发现可降低急性胰腺炎的风险并减轻胰腺损伤, 但其具体机制尚不明确。吲哚美辛是否可以抑制NF- κ B信号通路的激活还有待探索, 未来可进一步研究吲哚美辛在调节NF- κ B和Bcl-2/Caspase 3信号通路中的作用, 从而缓解急性胰腺炎引起的胃肠道损伤。

关键词

急性胰腺炎, NF- κ B信号通路, Bcl-2/Caspase 3信号通路, 吲哚美辛

Review and Hypothesis on the NF- κ B/Bcl-2/Caspase 3 Signaling Pathway and the Mechanism of Action of Indomethacin: Research on the Potential Mechanism of Gastrointestinal Dysfunction in Acute Pancreatitis

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Abstract

Acute pancreatitis is a severe inflammatory condition that can lead to gastrointestinal dysfunction and increased mortality. The NF- κ B signaling pathway plays a key role in the inflammatory response of acute pancreatitis; its activation induces the expression of various inflammatory cytokines and anti-apoptotic proteins, thereby exacerbating inflammation and affecting cell survival. The Bcl-2/Caspase 3 signaling pathway is also closely associated with the progression of acute pancreatitis, regulating the process of cell apoptosis. There is crosstalk between the NF- κ B and Bcl-2/Caspase 3 pathways—activation of NF- κ B can influence the expression of Bcl-2 family proteins, thereby modulating apoptosis. Indomethacin, a nonsteroidal anti-inflammatory drug, has been found to reduce the risk of acute pancreatitis and alleviate pancreatic injury, but its precise mechanism remains unclear. Whether indomethacin can suppress the activation of the NF- κ B signaling pathway warrants further investigation. Future studies may explore the role of indomethacin in modulating both the NF- κ B and Bcl-2/Caspase 3 pathways to mitigate gastrointestinal damage caused by acute pancreatitis.

Keywords

Acute Pancreatitis, NF- κ B Signaling Pathway, Bcl-2/Caspase 3 Signaling Pathway, Indomethacin

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1. 引言

急性胰腺炎(acute pancreatitis, AP), 是一种因多种因素引发胰酶提前激活, 进而对胰腺组织造成损伤的局部炎症性疾病, 其病情发展过程中可能会对其他器官功能产生影响, 也可能仅局限于胰腺本身[1]。AP 在临床上可分为轻型、中度重症和重症 3 种类型, 重症急性胰腺炎约占 AP 的 20%, 起病急、进展快, 临床病理变化复杂, 早期即可发生全身性炎症反应综合征(systemic inflammatory response syndrome, SIRS)、多器官功能障碍综合征(multiple organ dysfunction syndrome, MODS), 病死率高达 20%~30% [2] [3]。全球范围内, 急性胰腺炎的发病率为 23~49/10 万, 且该疾病复发风险较高[4]。在我国, 人口老龄化的趋势推动了胰腺炎发病率逐年上升[5] [6]。胰腺炎在消化系统疾病中的影响力和关注度显著提升, 对国民健康构成了严峻挑战。

2. 急性胰腺炎与胃肠道损伤

2.1. 急性胃肠道损伤及其可能机制

重症急性胰腺炎(severe acute pancreatitis, SAP)早期产生大量炎症介质、细胞因子和细菌毒素, 导致血

流动力学异常, 对心、肝、肾和胃肠道等器官造成损害, 严重时出现器官衰竭[7]。急性胃肠道损伤(acute gastrointestinal injury, AGI)是 SAP 患者最常见的并发症之一。由于胃肠道是全身菌群的储存库, 因此具有调节免疫和炎症功能等功能, AGI 发生时, 患者有胃肠功能障碍和黏膜损伤, 因此 AGI 的发生很可能与炎症反应、细胞凋亡、氧化应激、肠道菌群失调、微循环障碍等密切相关[8][9]。AGI 发生的机制一直处于不断探索中, 王敏等[10]发现 AGI 是 SAP 的独立危险因素。因此, 积极治疗 AGI 促进胃肠功能的恢复是缓解急性胰腺炎、降低死亡率、改善预后的关键。

2.2. 急性胃肠道损伤与紧密连接蛋白

健康的肠粘膜机械屏障由完整的上皮细胞和细胞旁连接复合物组成, 紧密连接(tight junction, TJ)蛋白属于细胞旁连接复合物。主要的 TJ 蛋白是咬合蛋白(Occludin)、闭合蛋白(Claudins)和闭合小环蛋白(zonula occluden, ZO), 它们增强肠道屏障以降低细胞的通透性。研究发现 SAP 发生时肠道组织 ZO-1、Claudin-1 和 Occludin 的 mRNA 和蛋白水平表达不足, 而 Claudin-2 过度表达, Claudin-2 蛋白导致细胞旁通透性增加[11]。这表明急性胰腺炎可引发肠道上皮细胞及细胞旁连接复合物的结构改变, 成为其诱发胃肠道功能障碍的重要机制之一。NF- κ B 信号通路激活可造成 TJ 发生改变, ZO 蛋白主要受 NF- κ B 信号通路和细胞因子调控。NF- κ B 激活后可通过会引发一系列炎症反应, 产生多种促炎细胞因子, 一些细胞因子可直接作用于肠道上皮细胞, 抑制紧密连接蛋白 ZO-1、Occludin 等的表达[12], NF- κ B 激活后也可以直接作用于紧密连接蛋白基因的启动子区域, 抑制其转录, 从而减少紧密连接蛋白的表达, 从可能的机制上讲, 炎症激活的 NF- κ B 形成 NF- κ B-CBP (cAMP-response element binding protein binding protein, CBP)复合物, 替代了 CREB (cAMP-response element binding protein, CREB)-CBP 蛋白复合物中的 CREB, 从而抑制 ZO-1 的表达。这种 ZO-1 表达的减少会加剧炎症损伤, 并加速病理过程[13][14]。除了在表达数量上的调控, NF- κ B 激活后, 也可通过相关信号通路促进 Occludin 的内化, 从而破坏紧密连接。例如, 在 TNF- α 诱导的屏障功能丧失中, Occludin 的内化被描述为 MLCK 肌球蛋白轻链激酶(myosin light-chain kinase, MLCK)依赖的过程, 而 NF- κ B 可正向调节 MLCK 的表达[15]。细胞凋亡可能也会降低紧密连接蛋白 ZO-1、Occludin 和 Claudin-1 的表达, 这可能是通过凋亡通路中半胱天冬氨酸特异性蛋白酶(cysteine aspartate specific proteinase, caspase)活化实现的, Caspase-3 是凋亡的关键执行者, 其激活与紧密连接蛋白表达下降有关, Caspase 的激活可能直接或间接地影响紧密连接蛋白的稳定性或转录水平, 从而导致其表达下调[16]。细胞凋亡和炎症反应在肠道炎症中相互交织, 炎症因子可诱导肠道上皮细胞凋亡, 而凋亡细胞释放的物质又可加剧炎症反应, 形成恶性循环。这种相互作用不仅加剧了肠道上皮细胞的损伤, 还导致紧密连接蛋白的持续下调, 使肠道屏障的完整性遭到破坏。AP 引发胃肠道紧密连接蛋白改变的机制颇为繁杂, 诸多环节的内在关联与作用原理尚未理清, 有待后续更深入且系统的研究进一步夯实证据。

3. 急性胰腺炎与 NF- κ B 信号通路

AP 的早期阶段的特征是胰腺内胰酶的病理激活导致胰腺组织的自我消化, 这种自消化将导致局部和全身炎症的激活[17]。多种信号通路贯穿于胰腺炎症的发生, 包括 PI3K/Akt、JAK/STAT 和 NF- κ B 等关键信号通路[18]。众所周知, NF- κ B 信号通路是一种成熟的炎症信号通路, 可在胰腺腺泡细胞中引发炎症[19]。NF- κ B 的激活起始信号主要包括促炎细胞因子(如 TNF- α 和 IL-1 β)、病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)以及损伤相关分子模式(damage-associated molecular patterns, DAMPs)。这些刺激信号最终转化为胰腺腺泡中可以激活 NF- κ B 信号途径的多种病理刺激, 例如钙过载, 激活 I- κ B 激酶(inhibitor of NF- κ B kinase, IKK), 导致 NF- κ B 抑制蛋白(inhibitor of NF- κ B, I κ B)磷酸化、p65/50 二聚体释放和核易位[18], 进而调控细胞的状态。NF- κ B 的激活是通过经典、非经典和不常见的非典型激

活途径来调控的, 刺激信号通过其相应的受体激活 IKK 复合体, 导致 I κ B 蛋白的磷酸化和随后的泛素化降解。I κ B 的降解使得 NF- κ B 二聚体得以释放并转移到细胞核内, 激活目标基因的转录[20][21]。NF- κ B 活化是 AP 中的关键炎症事件[22]。活化的 NF- κ B 作为转录因子发挥作用, 可以诱导促炎细胞因子、生长因子、趋化因子、粘附分子、环氧化酶(cyclooxygenase 2, COX2)和抗凋亡蛋白(如 Bcl-XL、Bcl-2)的转录[23]-[25]。通过 NF- κ B 激活从腺泡细胞释放的细胞因子有助于产生初始信号, 进而导致中性粒细胞和淋巴细胞浸润到胰腺和肠道中, 从而放大炎症反应[26]。一方面加剧各种细胞因子、趋化因子、粘附分子、氧自由基、血小板激活因子(platelet-activating factor, PAF)和内皮素的释放。另一方面, 这些释放的细胞因子以及其他信号分子又通过高度特异性的受体结合模式激活 NF- κ B [27]。造成 NF- κ B 过度激活, 形成炎症风暴。

4. 急性胰腺炎与 Bcl-2/Caspase 3 信号通路

4.1. Bcl-2 蛋白家族和 Caspase 3 蛋白

B 细胞淋巴瘤 2 (B-cell Lymphoma 2, Bcl-2)蛋白家族成员是具有促凋亡和抗凋亡活性的关键调节因子。这些调节因子在健康细胞中保持着精细、微妙的平衡[28]。Bcl-2 家族蛋白被分为 3 个亚族。以 Bcl-2 和 Bcl-XL 为代表的抗凋亡和促存活蛋白, 以 BAX 和 Bak 为代表的促凋亡蛋白, 以 BAD 和 BID 为代表的促凋亡 BH3-only 蛋白[29]。Bcl-2 家族蛋白发挥各自功能机制有所不同, 其中 Bcl-2 通过与 BAX 形成异源二聚体来抑制细胞凋亡[30], 促凋亡蛋白(如 Bax、Bak)通过促进细胞色素 c 的释放, 激活 Caspase 级联反应, 最终导致细胞凋亡[31][32], Bax 可以插入线粒体外膜, 形成孔道, 促进细胞色素 c 的释放[33], Bak 可破坏线粒体外膜的稳定性[34], 促进细胞色素 c 的释放。Caspase 3 是凋亡通路中的关键执行者, 它通过蛋白水解切割将多种底物转化为凋亡相关蛋白, 从而导致细胞结构和功能的破坏, Bcl-2 家族蛋白通过调节线粒体凋亡通路间接调控 Caspase 3 的活性[35]。

4.2. 急性胰腺炎与 Bcl-2/Caspase 3 信号通路联系

细胞凋亡在 AP 的发生发展中起关键作用, 胰腺腺泡细胞凋亡作为一种防御机制来防止胰腺坏死的发展。凋亡和坏死是 AP 时胰腺腺泡细胞死亡的两种主要方式, 二者最大的区别是凋亡细胞形成凋亡小体后很快被巨噬细胞吞噬, 不引起或极少引起炎症反应。在 AP 中, 抗凋亡蛋白的上调是一个常见的现象。宋凯峰等指出这些抗凋亡蛋白通过稳定线粒体膜电位, 防止线粒体去极化, 和 ATP 耗竭来保护胰腺腺泡免于坏死, 而不是防止凋亡, 同时还发现 Bcl-xL/Bcl-2 抑制剂能增强胆囊收缩(cholecystokinin, CCK)诱导的细胞坏死, 但不能增强细胞凋亡。进一步说明了 Bcl-xL/Bcl-2 抑制会加重急性胰腺炎, 而 Bcl-xL/Bcl-2 上调是预防或减轻胰腺炎坏死的一种策略[36]。但是在 Jacek J Litewka 等实验中证明使用 Bcl-2 抑制剂维奈托克(Venetoclax)选择性抑制 Bcl-2 可促进细胞凋亡、减少坏死并改善 AP 的预后[37]。很明显这两种观点截然相反, 这可能与胰腺炎模型种类、Bcl-2 抑制剂种类不同及胰腺炎模型处于不同阶段有关。这些研究说明 Bcl-2 家族蛋白与 AP 病程发展中胰腺损伤密切相关。

5. NF- κ B 信号通路与 Bcl-2/Caspase 3 信号通路联系

5.1. 细胞凋亡

凋亡通路主要包括外源性通路和内源性通路。外源性通路主要由死亡受体介导, 如 Fas 受体与 Fas 配体结合后, 可激活下游的 Caspase 8, 进而激活 Caspase 3 等效应 Caspase, 导致细胞凋亡。内源性通路则主要由线粒体介导, 当细胞受到各种应激信号如 DNA 损伤、缺氧等刺激时, Bcl-2 家族蛋白的平衡被打破, 促凋亡蛋白如 Bax、Bak 等被激活, 导致线粒体外膜通透性增加, 细胞色素 c 释放到细胞质中, 与凋

亡蛋白酶激活因子-1 (apoptotic protease activating factor-1, Apaf-1)结合形成凋亡小体, 激活 Caspase 9, 进而激活下游的效应 Caspase, 最终导致细胞凋亡。此外, 还有非 Caspase 依赖的凋亡途径, 如通过凋亡诱导因子(apoptosis-inducing factor, AIF)等蛋白介导的细胞核 DNA 损伤, 也可诱导细胞凋亡[35]。

5.2. NF- κ B 信号通路与 BCL-2/Caspase 3 信号通路的交互

多种信号参与 BCL-2/Caspase 3 信号通路的激活, 包括 PI3K/AKT 信号通路、NF- κ B 信号通路、ERK 信号通路和/或 JAK/STAT 信号通路等, 这表明 NF- κ B 信号通路与 Bcl-2/Caspase 3 信号通路存在着密切的联系[38]。NF- κ B 可作为程序性细胞死亡的抑制剂[39] [40]。NF- κ B 激活后可诱导 Bcl-XL、A1/Bfl-1、细胞凋亡抑制剂(inhibitor of apoptosis, IAP)等多种抗细胞凋亡蛋白表达[25], 这些抗细胞凋亡蛋白会通过各自途径抑制细胞凋亡。NF- κ B 还可以通过多种途径诱导细胞凋亡, 如通过表达靶基因产物 TNF- α , TNF- α 产生后通过外源性凋亡途径诱导细胞凋亡[41]。NF- κ B 激活后调控细胞凋亡机制复杂, 除了通过调控抗凋亡基因的表达和抑制凋亡信号通路的激活来拮抗刺激信号诱导的细胞凋亡外, 还取决于多种因素的综合影响。在 SAP 大鼠模型中, 大鼠肠道 BAX 表达增加和 Bcl-2 减少, 这与 NF- κ B 抗凋亡作用似乎矛盾, 造成这种相反结论的原因有多种, 例如, 在 SAP 的极端环境下, NF- κ B 抗凋亡的保护性作用可能被其自身驱动的剧烈炎症所淹没和压倒, NF- κ B 的过度激活产生海量 TNF- α 等因子, 这些因子强烈激活 Caspase 8 和 Bid/Bax 通路, 导致促凋亡蛋白在功能和表达上占据主导地位, 压倒了 NF- κ B 诱导的抗凋亡作用, 从而引发细胞凋亡[42] [43]。这为缓解 AP 患者肠道损伤提供了新思路, 通过抑制 NF- κ B 过度激活来恢复 NF- κ B 抗凋亡的作用, 减轻急性胰腺炎时肠道损伤。

6. 假说构建与论证

在 AP 病程中, 活化的 NF- κ B 驱动参与炎症的基因表达, 也参与驱动细胞存活的基因表达, 调节腺泡细胞凋亡和坏死。在 SAP 中, 通过 NF- κ B 过度激活的炎症因子加剧炎症反应, 进一步造成胰腺和其他器官的损伤, 包括肠道的损伤。AP 肠道炎症的发生被认为与血液循环紊乱、炎症因子和胃肠道激素失调有关。然而, 具体机制尚无完全阐明, 炎症反应在 AP 肠道损伤的发展和预后中起着至关重要的作用[44]。刘元启等[45]证明, 肠系膜淋巴管结扎可有效阻止肠道炎症介质进入体循环, 从而限制其在肠道内的积累。因此, SAP 期间, 会诱导炎症介质过度释放和免疫反应过度, 从而加剧肠道损伤。宋秀等研究发现, 在 SAP 合并胃肠功能障碍大鼠模型的肠道中存在大量 NF- κ B p65 阳性细胞[46], 这表明在 SAP 初期, 肠黏膜中 NF- κ B 的早期和显著激活。因此 NF- κ B 信号通路在急性胰腺炎炎症反应致胃肠道功能障碍中很可能发挥重要的作用。除了 NF- κ B 信号通路在胃肠道功能障碍中发挥重要的作用外, 是否还有 Bcl-2/Caspase 3 家族蛋白参与其中呢? 目前针对急性胰腺炎通过 Bcl-2/Caspase 3 信号通路造成胃肠道损伤的研究过少, 白金霞等研究发现在 L-精氨酸诱导的 SAP 小鼠模型中, 与正常对照组相比, 小肠组织中抗凋亡蛋白 Bcl-2 和 Bcl-xL 的 mRNA 表达水平显著降低, IL-22 通过激活 STAT3 信号通路, 上调抗凋亡蛋白 Bcl-2 和 Bcl-XL 的表达, 保护肠道屏障功能[47]。齐周等[48]研究发现, 大黄素可通过调节 BAX/Bcl-2/Caspase 3 信号通路作为预防急性胰腺炎肠道屏障损伤的潜在药物, SAP 诱导后的大鼠肠道 BAX 表达增加和 Bcl-2 减少, 经典的 BAX/Bcl-2/Caspase 3 通路可能参与肠道屏障损伤。因此, 通过调节 Bcl-2/Caspase 3 信号通路, 可能使急性胰腺炎造成的急性胃肠道损伤得到有效改善。吲哚美辛(indomethacin, IND)是临床上常见的非甾体类抗炎药(nonsteroidal anti-inflammatory drugs, NSAIDs)。多数研究证实吲哚美辛可以降低患者 ERCP 术后胰腺炎(post-ERCP pancreatitis, PEP)的风险[49] [50]。众多动物试验发现吲哚美辛可以减轻 SAP 大鼠的胰腺损伤[51] [52]。然而, 吲哚美辛预防 AP 造成胰腺和其他器官损伤的具体机制尚不明确。非甾体抗炎药发挥抗炎作用的经典途径主要是通过抑制环氧合酶来实现的, 特异性阻环氧合酶途径似乎对胰

腺炎的炎症情况无明显保护作用, 所以吡啶美辛很有可能通过独立于环氧合酶的非经典途径发挥其对胰腺炎的保护作用。有研究发现吡啶美辛可以抑制 KBM-5 细胞(人类髓系白血病细胞系, 具有单核细胞分化特征)中 NF- κ B 的激活[53]。在 SAP 的极端环境下, 大量 NF- κ B 的激活总效应可以造成促凋亡因素的升高, 压倒其抗凋亡效应。所以通过抑制 NF- κ B 的大量激活来降低 Bcl-2/Caspase 3 通路中促凋亡蛋白表达很可能成为吡啶美辛缓解急性胰腺炎胃肠道损伤的一种途径。

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